Steroid Dysregulation and Stomatodynia (Burning Mouth Syndrome)

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In their Focus Article, Woda et al[1] state that stomatodynia (burning mouth syndrome) is a neuropathic disorder involving mostly the peripheral nervous system (PNS)[2] but sometimes also the central nervous system (CNS).[3] They note that the causes of these neuropathic disorders are unknown and hypothesize that changes in steroid levels are involved in the occurrence and/or persistence of stomatodynia, with glucocorticoids contributing to the occurrence of stomatodynia and low neuroactive steroid levels (related to age in women) preventing recovery.

Glucocorticoids and Stomatodynia

Woda et al[1] observe that stomatodynia patients are often stressed and anxious and that high basic salivary cortisol levels have already been reported in patients who suffered from stomatodynia for more than 6 months.[4] However, this increase in cortisol levels was moderate (1.4 times higher than the mean value of the control group) and the diurnal rhythm of cortisol release was still conserved.

Chronic administration of high doses of glucocorticoids is able to induce changes in morphology and chemistry of CNS neurons, mainly of the hippocampus, prefrontal cortex, and amygdala, not only by itself but mostly because it induces an excessive release of the toxic excitatory amino acid glutamate. However, in the case of stress, these changes seem to be largely reversible even if chronic stress lasts for weeks, because of endogenous brain-protecting factors so that memory impairments linked to stress alone are rare.[5]

As far as the PNS is concerned, no neuropathy caused by stress (nor by hypercorticism, such as in Cushing syndrome) has been reported. Moreover, why should cortisol be toxic only to small-diameter nociceptive fibers in the oral region and not to thin nerve fibers elsewhere? Symptoms of stomatodynia are restricted to regions which are in contact with saliva, so one explanation could be that salivary glands are able to concentrate cortisol so that cortisol levels are higher in saliva than in blood, encounting for mouth-restricted toxicity. However, until now salivary cortisol has always been considered to reflect free blood cortisol concentration. On the other hand, inflammatory cytokines present in saliva could be responsible for mouth symptomatology, but reports in stomatodynia are controversial, with either increased secretion of interleukin 2 and 6[6] or no difference between stomatodynia and the control group.[7] Unfortunately, animal models are lacking to test all of the pathophysiological hypotheses bearing on stomatodynia, and particularly the toxicity of cortisol on thin fibers innervating the tongue and mouth mucosa. Regardless, it could be interesting to measure cortisol levels in a larger number of patients in order to confirm the persistence of a diurnal rhythm of secretion, to compare serum and salivary concentrations, and to evaluate the hypothalamic-pituitary-adrenal (HPA) axis reactivity through dynamic tests in stomatodynia.

Neuroactive Steroids and Stomatodynia

Several observations have demonstrated that the CNS and PNS are able to synthesize and metabolize neuroactive steroids. These neuroactive steroids include steroids produced de novo from cholesterol by the nervous system (termed neurosteroids) and hormonal steroids coming from gonads and adrenals, that can act directly or need to be further metabolized in order to be active in the nervous system. Their mechanisms of actions can involve

classical intracellular steroid receptors, but rapid actions occur at the membrane level, via specific membrane receptors, or through an interaction with receptors for neuromediators or ion channels.[8]

Neuroactive steroids are known to exert promyelinating and neuroprotective effects in the PNS.[9] But there is now evidence that allopregnanolone (3α-hydroxy-5α-pregnan-20-one) and also synthetic reduced pregnane and androstane compounds have potent analgesic effects in peripheral neuropathies (even against inflammatory pain) by positively modulating gamma-amino butyric acid type A ($GABA_A$) receptors, and by blocking low-voltage T-type calcium channels.[10]

Stomatodynia often occurs in postmenopausal women, when sex-steroid levels and particularly progesterone, one source of neuroactive steroids, fall dramatically. However, hormone replacement therapy does not seem to influence the course of the illness. Another way to treat stomatodynia could consist either in administrating neuroactive steroids directly on the tongue or in stimulating local neurosteroid synthesis.

Local Application of Neuroactive Steroids

Because of their neuroprotective, trophic, and antinociceptive properties, neuroactive compounds such as progesterone or allopregnanolone could be administered on the tongue. Dehydroepiandrosterone (DHEA), but not its sulfated ester, which is able to induce hyperalgesia in different animal models, could also be tested, as it is an antioxidant and is useful in treating rat diabetic neuropathies.[11] However, no antinociceptive property of DHEA has been demonstrated yet. Recently, a selective estrogen receptor beta agonist (Erb-131) has been shown to be effective in several animal models of pain.[12]

Stimulation of Local Neurosteroidogenesis

In the PNS, Schwann cells express the enzymes that are necessary for the synthesis of pregnenolone and progesterone, but the presence of sensory nerve fibers is necessary for their full activity. They are also able to further metabolize native steroids into 5α- and 3α-hydroxy-5α-reduced derivatives. Classical receptors for progesterone and estrogens have been demonstrated in rat sciatic nerve and Schwann cells, while androgen receptors have been detected in the endoneurium of sciatic nerve (not in Schwann cells). $GABA_A$ and peripheral benzodiazepine receptors, now termed Translocator Protein (18 kDa) (TSPO), are also expressed into the PNS.[9]

With regard to stomatodynia, two questions should be elucitated: the site of neurosteroid synthesis and the way of enhancing their production. As demonstrated by immunohistochemistry in human tongue biopsies,[2] subpapillary nerve bundles are mainly composed of unmyelinated C fibers, but thinly myelinated Aδ fibers are also present and might be able to synthetize neurosteroids locally. On the other hand, interactions between peripheral nerve injury and neurosteroid biosynthesis in the CNS have already been described. Indeed, rat sciatic nerve ligation and inflammatory pain in the paw enhance the production of pregnenolone and 5α-reduced neurosteroids in the dorsal horn of the spinal cord.[13,14] Pregnenolone promotes cytoskeleton development by stimulating microtubule formation[15] and regulates neuronal plasticity linked to the pathogenesis of chronic pain, while 5α-reduced neurosteroids play a role in the control of nociception through a prolongation of $GABA_A$ receptor-mediated synaptic currents. Finally, neurosteroidogenesis at the CNS level might represent an adaptative response of the body to chronic peripheral neuropathies. In the case of stomatodynia, one could hypothesize that the synthesis of neurosteroids occurs in the trigeminal brainstem sensory complex, but for unknown reasons this synthesis should be too low to be beneficial.

Stimulating neurosteroid synthesis at the tongue level could be a therapeutic option in stomatodynia. Among factors involved in the regulation of neurosteroidogenesis, peripheral benzodiazepine receptors TSPO seem to play a major role. They are present in non-neuronal and immune (macrophages) cells and have roles in energy metabolism, cell survival and growth, and steroid production. In the PNS, TSPO receptors are expressed by Schwann cells; however, they appear in dorsal root ganglion neurons following injury to the sciatic nerve.[16] They facilitate cholesterol transport from intracellular stores to inner mitochondrial membranes, where the enzyme responsible for the transformation of cholesterol into pregnenolone (first step of neurosteroid synthesis) is located.[17]

Benzodiazepines exert their effects by interacting with two types of receptors: $GABA_A$ receptors and mitochondrial TSPO. Clonazepam has a higher affinity for the $GABA_A$ than the TSPO receptor. Topical application of this benzodiazepine has been shown to be effective in stomatodynia patients.[18] The beneficial action of clonazepam might be related to its interaction with local $GABA_A$ receptors and to a lesser extent to neurosteroid synthesis

through the TSPO receptor. Thus, the topical application of a pure agonist of these receptors might be a promising treatment of stomatodynia. In the rat brain, the anxiolytic etifoxine has been shown to bind to the TSPO receptor and stimulate neurosteroid production.[19] In the PNS, after a cryolesion of the rat sciatic nerve, the local application of etifoxine was able to promote axonal regeneration, control neural inflammation by reducing the number of macrophages, and improve functional recovery.[20] It might be a good candidate for a topical treatment of stomatodynia.

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